Review Article

Non-colorectal non-neuroendocrine liver metastasis: a narrative review of surgical treatment

Celeste Del Basso[1], Sofia Usai[2], Giovanni Battista Levi Sandri[3]^

[1]Service de Chirurgie Viscérale Digestive Minimale Invasive, Hôpital Antoine Beclere, Clamart, France; [2]Department of Surgical Sciences, Policlinico Umberto I, Sapienza University of Rome, Rome, Italy; [3]General Surgery, Santa Scolastica Hospital Cassino, Lazio, Italy

Contributions: (I) Conception and design: GB Levi Sandri; (II) Administrative support: GB Levi Sandri; (III) Provision of study materials or patients: S Usai, C Del Basso; (IV) Collection and assembly of data: S Usai, C Del Basso; (V) Data analysis and interpretation: S Usai, C Del Basso; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Giovanni Battista Levi Sandri. General Surgery, Santa Scolastica Hospital Cassino, Lazio, Italy. Email: gblevisandri@gmail.com.

Background and Objective: The liver is the main site of metastatic disease, and cancer metastases remain the main limit to successfully managing the malignant disease. Liver resection (LR) for the treatment of metastatic cancer has been described for over a hundred years and is widely accepted. The role of surgery in managing non-colorectal non-neuroendocrine liver metastasis (NCNNLM), evidence is still lacking due to different factors: the paucity of cases, the wide variety of histological subtypes of the primary disease and its biological behavior, and the absence of prospective studies.

Methods: We performed a narrative review of peer-reviewed articles related to the surgical outcomes of NCNNLM. The aim of this review is determining the utility of surgery in NCNNLM, with attention to minimal invasive LRs. We analyzed the role of LR for NCNNLM according to the different cancers: digestive and non digestive.

Key Content and Findings: NCNNLM encompass a huge spectrum of histologic appearances. LR for limited NCNNLM may offer a curative option, but liver recurrence occurs frequently. Our ability to significantly predict the outcome is poor.

Conclusions: The cytotoxic chemotherapy and biologic agents have significantly altered the surgical treatment of LM. The latter treatments can convert inoperable patients into operable ones, with a clear relationship between the degree of resectability in patients judged inoperable at referral and the rate of response to the treatment scheme.

Keywords: Pancreatic cancer; gastric cancer (GC); melanoma; breast cancer; ovarian

Submitted Jan 31, 2022. Accepted for publication Aug 24, 2022.

doi: 10.21037/cco-22-13

View this article at: https://dx.doi.org/10.21037/cco-22-13

Introduction

Malignant tumors are likely to spread, leading to the development of metastases. After the lymph nodes, the liver can be considered the most common site of metastatic spread of abdominal tumors. Liver resection (LR) for metastatic cancer has been reported for over a century and is widely accepted. In addition, technical advances, technological innovation, and patient selection have remarkably improved the safety of liver surgery and let push the boundaries with extensive LR becoming more feasible (1). To date, LR is considered the gold standard for the treatment of patients with colorectal metastases limited to the liver, achieving 5- and 10-year survival rates of up to 60% and 20%, respectively (2). The liver is the main

^ ORCID: 0000-0002-7893-5047.

Table 1 The search strategy summary

Items	Specification
Date of search	31/12/2020
Databases and other sources searched	MedLine
Search terms used	Liver Resection; non-colorectal; non-neuroendocrine; gastric; melanoma; pancreatic breast; ovarian;
Timeframe	1960–31/12/2020
Inclusion and exclusion criteria	Only English study

site of metastatic disease, and cancer metastases remain the main limit to successfully managing the malignant disease. The most common cancer that metastasizes to the liver is colorectal cancer due to the rich portal and arterial blood supply and abdominal lymphatic channels. To date, the 5-year survival after surgery for colorectal liver metastases (LM) has been variously reported as 40–58% (3). Management of neuroendocrine LM is challenging, but LR is widely accepted, and there is sufficient evidence of its effectiveness. Concerning the role of surgery in managing non-colorectal non-neuroendocrine liver metastasis (NCNNLM), evidence is still lacking due to different factors: the paucity of cases, the wide variety of histological subtypes of the primary disease and its biological behavior, and the absence of prospective studies (4). Thanks to improvement in surgical and anesthetics techniques, the interest in liver surgery in NCNNLM has gained attention. We present the following article in accordance with the Narrative Review reporting checklist (available at https://cco.amegroups.com/article/view/10.21037/cco-22-13/rc).

Methods

The aim of this review is determining the utility of surgery in NCNNLM, with attention to minimal invasive LRs. We analyzed the role of LR for NCNNLM according to the different cancers: digestive and non digestive (*Table 1*).

Digestive

Gastric cancer (GC)

The GC is the 5th most diagnosed malignant cancer in the world. Mortality from GC still remains high, mainly because of its frequently advanced stage at diagnosis and because more than 50% of patients are more than 75 years. This makes GC the third leading cause of death from cancer (5). At the diagnosis, patients are frequently diagnosed with metastatic or with disseminated disease. According to some series, the 5-year survival in GC patients does not exceed 50% after surgery (6). So far, for patients with metastatic disease the standard of care is systemic chemotherapy with or without biologic agents. Overall survival (OS) and quality of life improved significantly with these treatments. OS using doublets or triplets with fluoropyrimidines, platinum derivatives and taxanes or anthracyclines reached 12 months (7). Concerning LM, they can be present both at the diagnosis either during the course of treatment and represent a key point in the prognosis of these patients undergoing first-line chemotherapy (8). According to this data, GC presenting with LM has been considered a very aggressive disease; in this context, the role of surgery, even for potentially resectable metastases has not been considered a standard approach. On the other hand, it is worth exploring the potential role of hepatectomy: the results of some meta-analysis show that hepatectomy for gastric LM provided survival benefit versus non hepatectomy at 1 year (OR =0.15; 95% CI: 0.10–0.22; P<0.00001), 3 years (OR =0.16; 95% CI: 0.10–0.27; P<0.00001), and 5 years (OR =0.13; 95% CI: 0.07–0.24; P<0.00001) (9). Careful patient selection is necessary. Another important independent prognostic factor is the presence of lymph node metastasis (10). Patients with N0 and N1 metastases have an apparent superior outcome prognosis versus N2 and N3 lymph node metastases. As far as we know, in colorectal LM, if radical excision can be achieved, the total number of repeat lesions is no longer considered as a predictor of OS. In contrast, in case of LR for GC metastases, a median survival of 5–8 months was obtained, with 15–50% and 19% survival at 1 year and 5 years respectively. Moreover, it has been demonstrated a strong relation between the number of LM and the OS. This may depend on the aggressive biologic behavior of GC. Encouraging results in term of OS come from Miyazaki

et al. (11), achieving a 5-year OS rate after LR of 39% and a median survival of 31 months in a series of 12 patients; 2 patients survived for more than 5 years. These results concern metachronous LM, with relatively long disease-free intervals. This study also concluded that, in case of solitary metastases and adequate tumor-free margins (>10 mm) there is a prognostic improvement (12). Encouraging results were reported by Cui *et al.* (9) after LR for metachronous metastases when compared to synchronous resection (OR =2.09; 95% CI: 1.21–3.60; P=0.008).

LR for gastric LM seems to be associated with a survival benefit especially in case of single metachronous LR, that tends to achieve a greater outcome than synchronous LR. This means that, despite the current statement, LR in very selected patients should be considered as a potential treatment option.

Pancreatic cancer

Pancreatic ductal adenocarcinoma (PDAC) represents the fourth most important cancer-related cause of death in Western nations and has an estimated 5-year survival rate of <8% (13). Recent epidemiological data show that in Western countries by 2030 it will become the second leading cause of cancer death (14). Furthermore, almost half of patients with PDAC are diagnosed with distant metastases and the liver with 37–41.9% is the most common site, of the initially diagnosed cases (15). In case of pancreatic cancer with synchronous LM, the prognosis with a median OS of only 5 months and a 5-year survival rate of less than 1% is extremely poor (16). As the primitive cancer, PDAC metastases have peculiar characteristics: they present abundant stroma known as 'desmoplasia', immune cells, vascular endothelial cells and cancer-associated fibroblasts (CAFs) (17). According to current guidelines for management of PDAC, systemic chemotherapy is the first choice for most metastatic cases, and surgery, in these patients, is contra indicated. Therapeutic regimes such as FOLFIRNOX or gemcitabine and nab-paclitaxel are currently proposed in palliative settings; these combination chemotherapy regimens showed to increase OS up to 11 months with a median of 8.5 months, compared to 7 or 6.7 months respectively with single agent gemcitabine (18). Concerning the role of surgery, resection of LM for locally resectable pancreatic cancer has hardly been practised. On the other hand, for LM surgery in colorectal cancer, neuroendocrine cancer and GC, studies have shown a significant improvement in long-term survival. Moreover, the improvement of surgical outcomes with mortality rates below 5% has increased the pool of patients who are candidates for pancreatic resective surgery associated with neoadjuvant therapy (19). The question of extending the "resectability criteria" for pancreatic cancer is still controversial. In some specialized centers, radical approaches have been described such an extended lymphadenectomy and arterial resections but, even in experts' hands, they have been shown not to be superior to standard resections. On the other side, the need to partially or completely resect the portal vein, the superior mesenteric vein for tumour infiltration drastically influences the morbidity and mortality of these patients. Furthermore, patients with vascular invasion treated by surgery has a superior median survival of 15 months compared to patients who undergo palliative therapy and nearly equal results of operated patients who did not need vascular resections (20). Up today, the gold standard of PDAC was surgery followed by adjuvant chemotherapy. The recent international consensus reported a new attitude: neoadjuvant treatment followed by surgery becoming the gold standard for all borderline PDAC; it's still not clear which is the best chemotherapeutic regimen to adopt in preoperative. Neoadjuvant treatment can make surgery challenging, but concerning post-operative results, the available literature showed comparable or even better results in the neoadjuvant treatment first compared with the upfront surgery approach (21). Concerning LR for metastatic PDAC, the first report in the literature dates from 1982 and report the larger series of metastasectomies by Morrow *et al.* (22). The feasibility of synchronous pancreatectomy and hepatectomy for metastatic PDAC has always been discussed with, on the one hand, encouraging results with mortality rates around <5% according to Yamada *et al.* (23). On the other side Gleisner *et al.* (24) reported a 30 day post-operative mortality up to 9.1% for patients undergoing synchronous liver metastasectomy for periampullary or pancreatic adenocarcinoma.

This data is quite discouraging compared to the 30 days post-operative mortality in the non-metastatic patients that is estimated at 4%, 5% or even 3% in the patients who underwent palliative bypass. In 1997, Takada *et al.* (25) observed the same high mortality rate in the group of patients with synchronous LM, and all metastatic patients died from multiple recurrent LM within a year. They concluded that patients treated by upfront surgery with primitive and simultaneous hepatic metastasis resection did not exhibit any survival improvement. An option of a cytoreductive

surgery was proposed in 2015 by Bahra *et al.* defining it as a supplement to palliative treatment to improve remaining quality of life (26).

Patients undergoing cytoreductive resection and subsequent standard palliative chemotherapy had an improved OS [hazard ratio (HR) =0.56; 95% CI: 0.36–0.87]. Concerning surgery, a total resection of all visible lesions is achieved (R0/M1) and showed relevant results (HR =0.39; 95% CI: 0.2–0.77). On the other side, the complications of this surgery remain superimposable in cases of extensive resections. Similar results are found in Klempnauer *et al.* (27) and Shrikhande *et al.* (28) in selected patients undergoing extensive resections including cases of peritoneal carcinosis after discussion with the interdisciplinary oncology committee and the patient. Long-term survival after pancreatic resection associated with LR for metastases was analysed by Andreou *et al.* (29) in 2018. These authors described postoperative morbidity and mortality rates of 50% and 5%, respectively, with OS 1 year, 3, 5 years were 41%, 13% and 7%, respectively. Moreover the 1-, 3-, and 5-year disease-free survival (DFS) rates were 39%, 9%, and 5%, respectively. Similar results come from Hackert *et al.* (30): in this series of 128 patients who underwent PDAC and metastases resection in case of oligometastatic stage (≤3 LM). The post-surgical morbidity and mortality for synchronous resection were 45% and 2.9%, respectively. The median OS after resection of 1 metastasis was 12.3 months in both groups. The long-term outcome showed a 5-year survival of 8.1% after surgery for both LM and 10.1% after resection of the interaortocaval lymph nodes. Yang provided further evidence that patients with oligometastatic pancreatic cancer may benefit from synchronous resection of the primary tumour and synchronous LM (31).

In case of synchronous resection, the median OS was 7.8 months. He concluded that PDAC patients with oligometastatic hepatic disease had a longer OS compared to non-oligometastatic synchronous resection patients, to patients treated by systemic chemotherapy and palliative patients (16.1 *vs.* 6.4 months, P=0.02; 16.1 *vs.* 7.6 months, P=0.02; 16.1 *vs.* 4.3 months, P<0.0001; respectively). Additional analysis indicated that the localised pancreas body/tail PDAC had a better OS in oligometastatic patients than in non-oligometastatic synchronous resection patients (16.8 *vs.* 7.05 months, P=0.0004) and systemic chemotherapy patients (16.8 *vs.* 8 months, P=0.003) (31). On the other side, neoadjuvant chemotherapy shows an increasing important role in selecting screening proper patients, it's the most powerful way to downstage lesions and eliminate micro metastases; neoadjuvant chemotherapy can eventually select appropriate candidates for synchronous surgery meaning that only those patients who have an effective response to neoadjuvant treatment might really benefit from aggressive surgery. Nappo *et al.* (21), in a recent metanalysis, concluded that neoadjuvant chemotherapy can have an important role even in border line resectable PDAC and that surgery, after neoadjuvant therapy, may be demanding on the one hand, but shows comparable if not better post-operative outcomes when compared to the upfront surgical approach; moreover a slight reduction in post-operative pancreatic fistula occurrence has been registered.

In conclusion, the aim of new PDAC surgery should probably not only be the selection of patients with the best chances for cure but the selection of patients that, with tumor resection, can achieve the longer survival with the better quality of life.

Gastrointestinal stromal tumour (GIST)

GIST accounts for 1% to 3% of gastrointestinal neoplasms and is the most frequent mesenchymal tumour of the gastrointestinal tract (32). Concerning the pathogenesis of the disease, an immunohistochemical reactivity for tyrosine-protein kinase (KIT) (CD117) is found in more than 90% of GIST cases, associated to mutations in KIT, or in some cases, platelet-derived growth factor receptor-a (PDGFRa) genes. This leads to constitutive activation of KIT (33). Surgical resection remained the primary treatment for LM from GISTs before the introduction of KIT inhibitors. However, surgery was not all the time curative and R0 resections were not always achieved. A 5-year OS rate of 30% was initially reported with a median survival of 36–47 months after LR (34). Discovery of imatinib mesylate (Gleevec; Novartis Pharmaceuticals, Basel, Switzerland), an inhibitor of KIT and PDGFRa tyrosine kinases, has dramatically changed the outcome of metastatic GIST patients. Response rates have been reported in up to 80%, with a median survival time which has increased to 5 years (35).

Nonetheless, complete response is rare and at least the half of patients develop resistance to imatinib as a result of secondary KIT or PDGFRa mutations approximately 2 years later (36). Even recurrence after a longer DFS (>5 years) has been reported. The most common sites of metastasis are peritoneum, liver or both. A true local

recurrence, to the priori surgery site, is unusual. Imatinib is the only recommended first line treatment in case of recurrent or metastatic GIST. Surgery is not indicated in case of metastatic disease but can be discussed and proposed to patient treatment in selected case to delay recurrence. So far, no randomised clinical trial has demonstrated the real benefit of this strategy.

Hypothetically, patients resected even grossly after medical treatment may achieve a longer DFS before secondary resistance develops. Imatinib can be administered to patients until surgery and resumed when the patient is able to start oral intake. However, sunitinib is discontinued 5 to 7 days before surgery and usually resumed only 2 weeks after surgery. In a study from Nunobe *et al.* (37) concerning hepatic resection for metastatic GIST tumors, an overall 5-year survival rate (including three patients with incomplete resection) of 34.0% and a median survival of 36 months, from the time of hepatic resection was reported.

This figure is comparable to previously reported series. Overall, morbidity and mortality were low for LR, with 10.3% and 2.5% severe complication and mortality rates, respectively. On the basis of univariate and multivariate analysis, patients who received only post-operative tyrosine kinase inhibitor (TKI) therapy had the most favourable outcomes. While extrahepatic disease at the time of LR predicted worse survival. In particular, the use of TKIs after surgery in treatment-naïve patients demonstrated a better OS. Furthermore, a shorter DFS was observed in patients with long exposure to TKIs before surgery (38). This is in line with the Haller *et al.* (39) approach, so treating recurrence of GIST with TKIs and leave surgery only for patients showing early resistance to systemic treatment. The determination of the optimal time point for surgery is therefore a critical event. The role of redo-surgery for recurrent disease within 6 months of the start of TKI therapy was emphasised by Cavnar *et al.* (40) in order to reduce the risk of TKI resistance for acquired mutations. With all the limitations of the small series that often mix GIST and sarcomas, we can provide evidence to support liver surgery together with systemic therapy in order to improve OS of patients with GIST metastasis with acceptable morbidity and mortality.

Non–digestive

Melanoma

Uveal melanomas are intraocular tumors originating from the uveal tract and represent the most common primary intraocular malignancy in adults. Uveal melanomas are usually initiated by a mutation in GNAQ or GNA11 but the underling mechanism is not completely clear. Almost half of patients develop metastatic disease, which usually affects the liver and is generally lethal by one year (41). One underling mechanism may be related to an early mutation in chromosome 3 and 8 and it strongly correlates to patient outcomes. The presence of monosomy 3 has been associated with an increased risk of liver metastasis (42).

Concerning cutaneous melanoma (CM), almost 31 were diagnosed with metastatic disease at the time of presentation, with more than half (56%) of patients presenting with a single synchronous metastasis and the other half with metachronous metastases (43,44). Although both ocular and CMs are tumors of melanocytes, their metastatic pattern is not the same. CMs spread initially via lymphatic pathway to regional lymph nodes or via the bloodstream to any organ, with liver being the third most common site of visceral metastasis (43). Uveal melanoma tends to present more often with isolated LM because, according to the model we have, the metastatic pathway spread is exclusively hematogenous as the uveal tract is devoid of lymphatics. On the other side, in comparison to CM, uveal melanoma metastases are less respondent to chemotherapy or immune checkpoint inhibitors and, above all in patients with melanoma liver metastasis.

As a consequence of the different metastatic behavior, the present literature comes from cases of LR for ocular melanoma metastases.

Data are still lacking and surgical resection was not well accepted as a therapeutic alternative because of the presence of other sites metastasis with a median survival of 4 to 6 months. According to Rose *et al.* (45) from the John Wayne Cancer Institute, complete surgical resection can be a curative option achieving long term survival in very selected patient. They report their experience on 24 patients (2% of all patients with melanoma disease) and they can achieve complete surgical removal of all metastatic disease in 18 patients (75%). DFS in the 24 resected patients was 12 months with a median OS of 28 months compared to median survival among patients with CM liver metastasis treated non operatively of 6 months with a 5-year survival of 4%. Similar results come from Ryu *et al.* (46), who reported a post-hepatectomy survival of 29 months and a 2- and 5-year survival rates of 59% and 42%, respectively. They did not find any difference in the median survival for primary ocular melanoma and primary CM. The main

factor associated with increased survival was tumor free resection margins (R0); other important factors that showed to improve post resection survival the number of liver lesions, a longer disease-free interval, lower tumor burden and systemic therapy.

In conclusion, surgical resection of melanoma LM, both uveal and cutaneous, can prolong survival in selected patients.

Breast cancer

Breast cancer still represent the leading cause of cancer related death in female patients. Is well known that breast cancer tends to metastasizes to the bony skeleton, lungs, liver, and brain via the circulation; as for other solid cancers, liver represents the third most common site for breast cancer (47). It has been reported that the 5-year survival rate for primary breast cancer is 99% but, in case of breast cancer with non-treated liver metastasis the OS becomes about 4–8 months (48). Systemic treatment still remain the main tool for treatment of metastatic breast cancer. Despite the great advances in systemic treatment such as chemotherapy, antiangiogenic treatment and targeted therapy (e.g., anti-hormonal therapy for patients with luminal breast cancer and Herceptin for HER-2-positive patients), the prognosis of breast cancer with liver metastasis treated this way is still poor, with a median survival time of only 25 months (49).

If we refer to recent guidelines, the 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4) state that "Local therapy should only be proposed in very selected cases of good performance status, with limited liver involvement, no extrahepatic lesions, after adequate systemic therapy has demonstrated control of the disease. Currently, there are no data to select the best technique for the individual patient (surgery, stereotactic radiotherapy, intrahepatic chemotherapy, etc.)" (50) while the 5th NCCN Guidelines that not even mentioned surgery in the past edition, statues that local therapy should only be proposed in very selected cases of good performance status, with limited liver involvement and no extrahepatic lesions, after adequate systemic therapy has demonstrated control of the disease. Currently, there are no data to choose the best treatment for the individual patient among surgery, stereotactic radiotherapy, intrahepatic chemotherapy, etc. (51). Selection criteria for choose the appropriate surgery candidates for breast cancer presenting with liver metastasis still need to be defined. Breast cancer LM is a challenging problem: in patients with metastases, approximately 90% is diagnosed with a multifocal disease and with extrahepatic localizations. These patients are not eligible for surgery. On the other side, even if mechanism if breast liver metastatisation is unclear, breast cancer LMs are associated with a particularly poor prognosis. This leads to prefer treatments with a minimal toxicity profile including systemic chemotherapy and LR. For the 10% of patients presenting with single or technically resectable LM encouraging results comes from some small retrospective studies. Prior to LR, patients have to been treated for primitive cancer. One of the first study comes from Adam *et al.* (48), with encouraging results liked to LR: the overall 5-year survival was 41%, with a 5-year DFS of 21%; untreated patients with breast cancer LM have a median survivals of approximately 3 to 6 months and even with systemic therapy, median survival is about 15 months. On multivariate analysis, R2 resection and prior failure to systemic chemotherapy were associated with worst survival. The number and size of LMs is not thought to predict outcome but in a multivariate analysis presented by He *et al.* (52), patients with >2-year intervals between breast surgery and breast cancer LM diagnosis (HR =0.178; 95% CI: 0.037–0.869; P=0.033), showed a significant trend towards better survival. The same study showed that patients who received Pringle maneuver during liver surgery had a longer OS (OS increase from 42.81 to 57.59 months). The role of lymphadenectomy is not clear while the stage of the primary disease appears to be irrelevant (53).

Data are still lacking but the results are encouraging. Liver exploration during surgery it's crucial in order to be sure that no metastatic lesion is missed. Open and laparoscopic surgery can both be safe and, in selected patients, laparoscopic surgery shows more favorable outcomes.

Testicular

The pattern of spreading for testicular cancer is known to be lymphatically to retroperitoneal lymph nodes and hematogenous to the pulmonary parenchyma but it may also spread to the liver. One of the first series with encouraging results in the management of hepatic testicular cancer metastasis is from Maluccio *et al.* (54), with 57 patients treated with LR. In 87% of cases LR was associated with others concomitant procedures. Complete surgical resection of all measurable disease is considered, in this study, the gold standard. It was associated with improvements in both DFS and OS after hepatectomy with

a survival rate of 78% at 3 years. The results coming from another series from Hahn *et al.* (55), were less encouraging with only 57 of the 2,219 patients who underwent post-chemotherapy retroperitoneal lymph node dissections for treatment of testicular carcinoma candidates for liver surgery for treatment of metastatic disease. In this small court of patients, the overall 5-year survival was 45%. Little is known about testicular cancer liver metastasis and more study are needed.

Ovarian

Ovarian cancer is actually an aggressive tumor and most patients are diagnosed at an advanced stage of disease. Ovarian cancer is the fifth cause of death for cancer among women, accounting for more deaths than any other cancer of the female reproductive system. The most common metastasis patterns of ovarian cancer LM are peritoneal dissemination, hematogenous metastasis and lymph node metastasis nevertheless, liver is one of the target organs of ovarian cancer LM (56).

Unfortunately, patients diagnosed with ovarian cancer are often young and frequently in advanced stages with metastatic disease. Upon the diagnosis of stage 3 or 4, patients may undergo cytoreductive operation, which includes hysterectomy, bilateral salpingo oophorectomy, omentectomy, and resection of all macroscopic metastatic lesions. In addition, about 40% of patients with advanced ovarian cancer have larger lesions in the upper abdomen, including the diaphragm, stomach and liver. Cytoreductive surgery is the major treatment option for ovarian carcinoma and has been proved to offer survival benefits when R0 resection is achieved. It can also be performed before chemotherapy or radiotherapy if R0 resection is not feasible (57). Secondary cytoreductive surgery has been suggested to have a survival benefit in selected platinum-sensitive patients been more efficient than chemotherapy, hormone therapy, or intraarterial chemoembolization (58).

The role of LR as part of cytoreductive surgery is still controversial. A review from Benedetti Panici *et al.* (59) reported life-threatening complications associated with diaphragmatic resection (P=0.004), hepatic resection (P=0.004), pancreatectomy (P=0.011) and biliary surgery (P=0.049). LR for ovarian cancer metastases was first described in 1976 (60). Researches gradually focused on this treatment even with encouraging results especially in very selected patients with a concomitant R0 cytoreductive surgery with an OS of 50.1 months significantly compared to patients that received only cytoreductive surgery without LR (61). There are few studies that demonstrated the safety of LR with no mortality within 30 days (62-64).

The association during cytoreduction of an LR has been described as feasible with acceptable morbidity and mortality. This treatment option could with a hepatic R0 improve OS. This means that when achieved, an R0 LR can significantly improve the prognosis of patients. Patients selection still remains crucial and bilateral liver lobes metastases is a contra-indication for surgery.

Thyroid

Both papillary and follicular (differentiated) thyroid carcinoma are considered among the most curable tumours. Compared to the incidence of thyroid nodules, they are quite rare and represent less than 1% of all human cancers. Differentiated thyroid carcinoma usually behaves in an indolent manner with low metastatic potential. This means that metastases from differentiated thyroid cancer are usually locoregional and they are frequently seen in cervical and mediastinal lymph nodes. In case of distant metastases, they are mainly seen in lung and bones with LM from differentiated thyroid cancer being quite rare, with a reported frequency of 0.5%. Distant metastases are the most important negative prognostic factor: they profoundly affect OS, with only 50% of surviving after 10 years (65). There are limited cases documented in literature. As reported in a study by Song *et al.* (66) only 10 cases have been documented in the literature; three males and seven females, with an average age of about 63 years (range from 32 to 85 years). Histological findings were: a papillary type in four patients, follicular type in five patients, and Hurthle cell thyroid cancer in one patient. In case of thyroid liver masses, the diagnosis can be done by standard imaging modalities, such as ultrasonography and CT, because LM are usually 131I negative. There are also 131I-positive metastases originating from extremely rare differentiated thyroid cancer: this kind of LM has a worst prognosis (67). Considering treatment options, the results of chemotherapy, partial hepatectomy, chemoembolization, radiofrequency ablation, liver radioembolization with 90Y microspheres are unfortunately non so promising.

On the other side, surgical resection of liver lesions has been reported to offer the best chance for prolonged survival (68). In conclusion, surgical treatment of thyroid

LM is justified by the favourable effect it has on the patient's prognosis and quality of life.

Renal cell

Renal cell carcinomas (RCC) comprise a heterogeneous group of malignant neoplasms arising from the nephron. RCC accounts for nearly 2% of all malignancies in developed countries and its incidence is increasing worldwide (69). The most common histologic variants include: clear cell RCC (ccRCC), papillary RCC (pRCC), and chromophobe RCC (chrRCC) and they represent the 75%, 10% and 5% of all kidney cancers, respectively (70). The metastatic pattern depends on histologic subtypes. For example, lung, adrenal, brain, and pancreatic metastases are more frequent in ccRCC; pRCC tends to present with lymph node and peritoneal metastases. Concerning LM, they were more common in chrRCC (71). LMs from RCC are present in almost 20% of cases and represent about 5–8% of secondary non-colorectal non-neuroendocrine liver tumors. LMs seem to be associated with a particularly poor prognosis and when they are present, about 25% are solitary and 75% are multiple (72). Concerning treatment options, as the primitive cancer is only little affected by radiotherapy or chemotherapy, surgical resection was longly considered the only curative treatment. Outcomes of surgery for metastatic RCC have mostly been investigated for pulmonary localizations because the lungs are a preferential metastatic site (73). Furthermore, LR has been performed in a small percentage of patients because development of liver metastasis is still considered a poor prognostic factor and a predictor of widespread disease. Data regarding the efficacy of surgical treatment of RCC LM are rarely reported. The Paul Brousse experience reported a series of 19 patients, with 14 (74%) of the 19 patients presenting with metachronous metastasis (74). The 3- and 5-year DFS rates were 25% and 25%, respectively; 3- and 5-year OS rates were 52% and 26%, respectively, with one patient alive 5 years following first hepatectomy. Thelen *et al.* (75), in their single center experience, reported a series of 31 patients with a 1-, 3- and 5-year OS rates were 82.2%, 54.3%, and 38.9%, respectively. In the big series of Adam *et al.* (76), metastases from urologic primary tumors represented the third largest subset and these primary tumor sites were associated with a 5-year survival of 48% and a median survival of 51 months, with renal cell LM associated with 38%—5-year survivals. Ruys *et al.* (77), in 2011, published another series of 33 patients, who underwent both resection (n=29) or local ablation (n=4) with an OS at 1 year, 3, and 5 years was 79%, 47%, and 43%, respectively. All the reported series tried to identify prognostic factors predicting long-term survival after resection of RCC LM. This good prognostic factors include male sex, a diameter of ≤5 cm, primary renal tumor, disease-free interval of >24 months, and R0 resection margins. The aim of determining precises prognostic factors is fundamental to select the best candidates for LR.

All the present data strongly support the recommendation that, in the absence of effective systemic therapies, LR should be considered a valid therapeutic tool to all patients with LM from renal cancer, provided that an R0 resection is feasible.

LR remains the only potentially curative option for patients with liver metastasis. Although there are no clear oncological indications several studies have shown overlapping results between LR for colorectal versus non-colorectal metastases (78,79).

Patient selection remains an area of debate. If we consider the progress made in liver surgery in recent years. First and foremost thanks to new technologies, such as minimally invasive, but also the possibility of parenchyma sparing surgery. The often better functional liver quality after chemotherapy in these patients and the progress in peri-operative anaesthesia. All these elements make it possible to increasingly push the indications for resection in patients who until a few years ago were considered out of surgical treatment. For these reasons, we believe that patient selection must be performed "ad personam" depending also on the experience of the centre proposing the surgical treatment.

Conclusions

NCNNLM encompasses a huge spectrum of histologic appearances. LR in case of limited NCNNLM may be considered an important curative treatment. These results could be achieved thanks to a better disease control due to new chemotherapies treatments. Moreover, a better knowledge in cancer biology and the improvement in surgical techniques with a better oncological outcome permitted to improve patients' survival.

Patients' selection remains the main predictor of recurrence and OS but more studies are needed to identify the reals predictors of outcome after LR for NCNNLM and to evaluate not only survival benefit but also quality of life and cost effectiveness. What we know is that the use of cytotoxic chemotherapy and biological agents strongly

influence LR, permitting to convert inoperable patients to operable ones. There is a clear correlation between the resectability rate in patients considered inoperable at presentation and the response rate to the therapeutic schedule. As for colorectal LM, LR itself confirmed similar safety. Liver surgery deeply changed in recent years and has become refined and more safety. The principal feature acting in reducing complications and mortality is lowering blood loss and blood transfusions.

Moreover, parenchymal sparing techniques, such as atypical resections for metastases, became important and permit to preserve liver volume and function with great advantages for the patients and the possibility of safe repetitive surgeries. LM represent one of the most frequent indications among malignances. The present data suggest the possibility that number of candidates for hepatectomy or ablation therapy for NCNNLM may increase among patients with initially unresectable tumors due to advances in chemotherapy and surgical technique. In particular, resection of LM from NCNN tumors is safe and that it may be promising strategy for prolonging survival in very selected patients.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Chinese Clinical Oncology* for the series "Hepatobiliary and Pancreatic Cancers: An Update of Surgical Treatments". The article has undergone external peer review.

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://cco.amegroups.com/article/view/10.21037/cco-22-13/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cco.amegroups.com/article/view/10.21037/cco-22-13/coif). The series "Hepatobiliary and Pancreatic Cancers: An Update of Surgical Treatments" was commissioned by the editorial office without any funding or sponsorship. GBLS serves as the unpaid Guest Editor of the series. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Harrison LE, Brennan MF, Newman E, et al. Hepatic resection for noncolorectal, nonneuroendocrine metastases: a fifteen-year experience with ninety-six patients. Surgery 1997;121:625-32.
2. Basso M, Corallo S, Calegari MA, et al. The impact of multidisciplinary team management on outcome of hepatic resection in liver-limited colorectal metastases. Sci Rep 2020;10:10871.
3. Bismuth H, Adam R, Lévi F, et al. Resection of nonresectable liver metastases from colorectal cancer after neoadjuvant chemotherapy. Ann Surg 1996;224:509-20; discussion 520-2.
4. Takemura N, Saiura A. Role of surgical resection for non-colorectal non-neuroendocrine liver metastases. World J Hepatol 2017;9:242-51.
5. Smyth EC, Nilsson M, Grabsch HI, et al. Gastric cancer. Lancet 2020;396:635-48.
6. Al-Batran SE, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. Lancet 2019;393:1948-57.
7. Smyth EC, Verheij M, Allum W, et al. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016;27:v38-49.
8. Chau I, Norman AR, Cunningham D, et al. Multivariate prognostic factor analysis in locally advanced and metastatic esophago-gastric cancer--pooled analysis from

three multicenter, randomized, controlled trials using individual patient data. J Clin Oncol 2004;22:2395-403.
9. Cui JK, Liu M, Shang XK. Hepatectomy for Liver Metastasis of Gastric Cancer: A Meta-Analysis. Surg Innov 2019;26:692-7.
10. Oki E, Tokunaga S, Emi Y, et al. Surgical treatment of liver metastasis of gastric cancer: a retrospective multicenter cohort study (KSCC1302). Gastric Cancer 2016;19:968-76.
11. Miyazaki M, Itoh H, Nakagawa K, et al. Hepatic resection of liver metastases from gastric carcinoma. Am J Gastroenterol 1997;92:490-3.
12. Minagawa M, Makuuchi M, Torzilli G, et al. Extension of the frontiers of surgical indications in the treatment of liver metastases from colorectal cancer: long-term results. Ann Surg 2000;231:487-99.
13. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70:7-30.
14. Rahib L, Smith BD, Aizenberg R, et al. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res 2014;74:2913-21.
15. van der Geest LGM, Lemmens VEPP, de Hingh IHJT, et al. Nationwide outcomes in patients undergoing surgical exploration without resection for pancreatic cancer. Br J Surg 2017;104:1568-77.
16. Kneuertz PJ, Cunningham SC, Cameron JL, et al. Palliative surgical management of patients with unresectable pancreatic adenocarcinoma: trends and lessons learned from a large, single institution experience. J Gastrointest Surg 2011;15:1917-27.
17. Takesue S, Ohuchida K, Shinkawa T, et al. Neutrophil extracellular traps promote liver micrometastasis in pancreatic ductal adenocarcinoma via the activation of cancer associated fibroblasts. Int J Oncol 2020;56:596-605.
18. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364:1817-25.
19. Tachezy M, Gebauer F, Petersen C, et al. Sequential neoadjuvant chemoradiotherapy (CRT) followed by curative surgery vs. primary surgery alone for resectable, non-metastasized pancreatic adenocarcinoma: NEOPA- a randomized multicenter phase III study (NCT01900327, DRKS00003893, ISRCTN82191749). BMC Cancer 2014;14:411.
20. Yekebas EF, Bogoevski D, Cataldegirmen G, et al. En bloc vascular resection for locally advanced pancreatic malignancies infiltrating major blood vessels: perioperative outcome and long-term survival in 136 patients. Ann Surg 2008;247:300-9.
21. Nappo G, Donisi G, Zerbi A. Borderline resectable pancreatic cancer: Certainties and controversies. World J Gastrointest Surg 2021;13:516-28.
22. Morrow CE, Grage TB, Sutherland DE, et al. Hepatic resection for secondary neoplasms. Surgery 1982;92:610-4.
23. Yamada H, Hirano S, Tanaka E, et al. Surgical treatment of liver metastases from pancreatic cancer. HPB (Oxford) 2006;8:85-8.
24. Gleisner AL, Assumpcao L, Cameron JL, et al. Is resection of periampullary or pancreatic adenocarcinoma with synchronous hepatic metastasis justified? Cancer 2007;110:2484-92.
25. Takada T, Yasuda H, Amano H, et al. Simultaneous hepatic resection with pancreato-duodenectomy for metastatic pancreatic head carcinoma: does it improve survival? Hepatogastroenterology 1997;44:567-73.
26. Bahra M, Pratschke J, Klein F, et al. Cytoreductive Surgery for Pancreatic Cancer Improves Overall Outcome of Gemcitabine-Based Chemotherapy. Pancreas 2015;44:930-6.
27. Klempnauer J, Ridder GJ, Piso P, et al. Is liver resection in metastases of exocrine pancreatic carcinoma justified? Chirurg 1996;67:366-70.
28. Shrikhande SV, Kleeff J, Reiser C, et al. Pancreatic resection for M1 pancreatic ductal adenocarcinoma. Ann Surg Oncol 2007;14:118-27.
29. Andreou A, Knitter S, Klein F, et al. The role of hepatectomy for synchronous liver metastases from pancreatic adenocarcinoma. Surg Oncol 2018;27:688-94.
30. Hackert T, Niesen W, Hinz U, et al. Radical surgery of oligometastatic pancreatic cancer. Eur J Surg Oncol 2017;43:358-63.
31. Yang J, Zhang J, Lui W, et al. Patients with hepatic oligometastatic pancreatic body/tail ductal adenocarcinoma may benefit from synchronous resection. HPB (Oxford) 2020;22:91-101.
32. Nishida T, Hirota S. Biological and clinical review of stromal tumors in the gastrointestinal tract. Histol Histopathol 2000;15:1293-301.
33. Joensuu H. Gastrointestinal stromal tumor (GIST). Ann Oncol 2006;17 Suppl 10:x280-6.
34. DeMatteo RP, Shah A, Fong Y, et al. Results of hepatic resection for sarcoma metastatic to liver. Ann Surg 2001;234:540-7; discussion 547-8.
35. Shi YN, Li Y, Wang LP, et al. Gastrointestinal stromal tumor (GIST) with liver metastases: An 18-year experience

from the GIST cooperation group in North China. Medicine (Baltimore) 2017;96:e8240.
36. Scaife CL, Hunt KK, Patel SR, et al. Is there a role for surgery in patients with "unresectable" cKIT+ gastrointestinal stromal tumors treated with imatinib mesylate? Am J Surg 2003;186:665-9.
37. Nunobe S, Sano T, Shimada K, et al. Surgery including liver resection for metastatic gastrointestinal stromal tumors or gastrointestinal leiomyosarcomas. Jpn J Clin Oncol 2005;35:338-41.
38. Xia L, Zhang MM, Ji L, et al. Resection combined with imatinib therapy for liver metastases of gastrointestinal stromal tumors. Surg Today 2010;40:936-42.
39. Haller F, Detken S, Schulten HJ, et al. Surgical management after neoadjuvant imatinib therapy in gastrointestinal stromal tumours (GISTs) with respect to imatinib resistance caused by secondary KIT mutations. Ann Surg Oncol 2007;14:526-32.
40. Cavnar MJ, Seier K, Curtin C, et al. Outcome of 1000 Patients With Gastrointestinal Stromal Tumor (GIST) Treated by Surgery in the Pre- and Post-imatinib Eras. Ann Surg 2021;273:128-38.
41. Jager MJ, Shields CL, Cebulla CM, et al. Uveal melanoma. Nat Rev Dis Primers 2020;6:24.
42. Bustamante P, Piquet L, Landreville S, et al. Uveal melanoma pathobiology: Metastasis to the liver. Semin Cancer Biol 2021;71:65-85.
43. Patel JK, Didolkar MS, Pickren JW, et al. Metastatic pattern of malignant melanoma. A study of 216 autopsy cases. Am J Surg 1978;135:807-10.
44. Tas F. Metastatic behavior in melanoma: timing, pattern, survival, and influencing factors. J Oncol 2012;2012:647684.
45. Rose DM, Essner R, Hughes TM, et al. Surgical resection for metastatic melanoma to the liver: the John Wayne Cancer Institute and Sydney Melanoma Unit experience. Arch Surg 2001;136:950-5.
46. Ryu SW, Saw R, Scolyer RA, et al. Liver resection for metastatic melanoma: equivalent survival for cutaneous and ocular primaries. J Surg Oncol 2013;108:129-35.
47. Hess KR, Varadhachary GR, Taylor SH, et al. Metastatic patterns in adenocarcinoma. Cancer 2006;106:1624-33.
48. Adam R, Aloia T, Krissat J, et al. Is liver resection justified for patients with hepatic metastases from breast cancer? Ann Surg 2006;244:897-907; discussion 907-8.
49. Zinser JW, Hortobagyi GN, Buzdar AU, et al. Clinical course of breast cancer patients with liver metastases. J Clin Oncol 1987;5:773-82.
50. Cardoso F, Senkus E, Costa A, et al. 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4)†. Ann Oncol 2018;29:1634-57.
51. Cardoso F, Paluch-Shimon S, Senkus E, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 2020;31:1623-49.
52. He X, Zhang Q, Feng Y, et al. Resection of liver metastases from breast cancer: a multicentre analysis. Clin Transl Oncol 2020;22:512-21.
53. Elias D, Maisonnette F, Druet-Cabanac M, et al. An attempt to clarify indications for hepatectomy for liver metastases from breast cancer. Am J Surg 2003;185:158-64.
54. Maluccio M, Einhorn LH, Goulet RJ. Surgical therapy for testicular cancer metastatic to the liver. HPB (Oxford) 2007;9:199-200.
55. Hahn TL, Jacobson L, Einhorn LH, et al. Hepatic resection of metastatic testicular carcinoma: a further update. Ann Surg Oncol 1999;6:640-4.
56. Nakayama K, Nakayama N, Katagiri H, et al. Mechanisms of ovarian cancer metastasis: biochemical pathways. Int J Mol Sci 2012;13:11705-17.
57. Pekmezci S, Saribeyoglu K, Aytac E, et al. Surgery for isolated liver metastasis of ovarian cancer. Asian J Surg 2010;33:83-8.
58. Elias D, Cavalcanti de Albuquerque A, Eggenspieler P, et al. Resection of liver metastases from a noncolorectal primary: indications and results based on 147 monocentric patients. J Am Coll Surg 1998;187:487-93.
59. Benedetti Panici P, Di Donato V, Fischetti M, et al. Predictors of postoperative morbidity after cytoreduction for advanced ovarian cancer: Analysis and management of complications in upper abdominal surgery. Gynecol Oncol 2015;137:406-11.
60. Brunschwig A. Hepatic lobectomy for metastatic cancer. Cancer 1963;16:277-82.
61. Bristow RE, Tomacruz RS, Armstrong DK, et al. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. J Clin Oncol 2002;20:1248-59.
62. Bacalbasa N, Dima S, Brasoveanu V, et al. Liver resection for ovarian cancer liver metastases as part of cytoreductive surgery is safe and may bring survival benefit. World J Surg Oncol 2015;13:235.
63. Merideth MA, Cliby WA, Keeney GL, et al. Hepatic resection for metachronous metastases from ovarian carcinoma. Gynecol Oncol 2003;89:16-21.
64. Luna-Abanto J, García Ruiz L, Laura Martinez J, et al.

Liver Resection as Part of Cytoreductive Surgery for Ovarian Cancer. J Gynecol Surg 2020;36:70-5.
65. Elisei R, Molinaro E, Agate L, et al. Are the clinical and pathological features of differentiated thyroid carcinoma really changed over the last 35 years? Study on 4187 patients from a single Italian institution to answer this question. J Clin Endocrinol Metab 2010;95:1516-27.
66. Song HJ, Xue YL, Qiu ZL, et al. Uncommon metastases from differentiated thyroid carcinoma. Hell J Nucl Med 2012;15:233-40.
67. Song HJ, Xue YL, Xu YH, et al. Rare metastases of differentiated thyroid carcinoma: pictorial review. Endocr Relat Cancer 2011;18:R165-74.
68. Niederle B, Roka R, Schemper M, et al. Surgical treatment of distant metastases in differentiated thyroid cancer: indication and results. Surgery 1986;100:1088-97.
69. Parkin DM, Bray F, Ferlay J, et al. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74-108.
70. Choueiri TK, Motzer RJ. Systemic Therapy for Metastatic Renal-Cell Carcinoma. N Engl J Med 2017;376:354-66.
71. Dudani S, de Velasco G, Wells JC, et al. Evaluation of Clear Cell, Papillary, and Chromophobe Renal Cell Carcinoma Metastasis Sites and Association With Survival. JAMA Netw Open 2021;4:e2021869.
72. Janzen NK, Kim HL, Figlin RA, et al. Surveillance after radical or partial nephrectomy for localized renal cell carcinoma and management of recurrent disease. Urol Clin North Am 2003;30:843-52.
73. Pfannschmidt J, Hoffmann H, Muley T, et al. Prognostic factors for survival after pulmonary resection of metastatic renal cell carcinoma. Ann Thorac Surg 2002;74:1653-7.
74. Aloia TA, Adam R, Azoulay D, et al. Outcome following hepatic resection of metastatic renal tumors: the Paul Brousse Hospital experience. HPB (Oxford) 2006;8:100-5.
75. Thelen A, Jonas S, Benckert C, et al. Liver resection for metastases from renal cell carcinoma. World J Surg 2007;31:802-7.
76. Adam R, Chiche L, Aloia T, et al. Hepatic resection for noncolorectal nonendocrine liver metastases: analysis of 1,452 patients and development of a prognostic model. Ann Surg 2006;244:524-35.
77. Ruys AT, Tanis PJ, Nagtegaal ID, et al. Surgical treatment of renal cell cancer liver metastases: a population-based study. Ann Surg Oncol 2011;18:1932-8.
78. Lok HT, Fung AKY, Chong CCN, et al. Comparison of long-term survival outcome after curative hepatectomy between selected patients with non-colorectal and colorectal liver metastasis: A propensity score matching analysis. Asian J Surg 2021;44:459-64.
79. Račkauskas R, Baušys A, Sokolovas V, et al. Short- and long-term outcomes of surgery for colorectal and non-colorectal liver metastasis: a report from a single center in the Baltic country. World J Surg Oncol 2020;18:164.

Cite this article as: Del Basso C, Usai S, Levi Sandri GB. Non-colorectal non-neuroendocrine liver metastasis: a narrative review of surgical treatment. Chin Clin Oncol 2022;11(4):28. doi: 10.21037/cco-22-13